Amendments to the Drawings:

The attached replacement sheets of drawings includes changes to Figs. 1-20 and replace the original sheets including Figs. 1-20. These sheets correct the figures to include the English translations of the Japanese characters. No new matter has been added.

Attachments following last page of this Amendment:

Replacement Sheets (20 pages)

REMARKS

Claims 1, 2, 4, 5, 9-13, 17, 18, 23, 28, 30, and 33 are canceled without prejudice; claims 3, 6-8, 14-16, 21, 22, 29, 31, and 32 are currently amended; and new claims 34-46 are added. Support for the amendments and new claims can be found throughout the specification as filed, e.g., at page 76, lines 6-17, and page 123, lines 13-15. No new matter has been added. Claims 3, 6-8, 14-16, 21, 22, 29, 31, 32, and 34-46 are pending and under examination, whereas claims 19, 20, and 24-27 are pending but withdrawn as drawn to a non-elected invention.

Drawings

The drawings were objected to as containing Japanese language characters. Corrected drawings submitted herewith replace the Japanese characters with their English translations.

Specification

The disclosure was objected to as containing an embedded hyperlink or other form of browser-executable code at page 125, line 5. Applicants have amended the specification to delete the hyperlink or browser-executable code.

Claim Objections

Claim 28 was objected to for a typographical error. This claim has been canceled, thus mooting the objection.

Claim 15 was objected to for failing to limit the subject matter of previous claim 9. Applicants have canceled claim 9 and amended claim 15 such that it no longer depends from claim 9.

35 USC § 101

Claims 1-6, 10-14, 16-18, and 28-33 were rejected as allegedly directed to non-statutory subject matter. Claims 1, 2, 4, 5, 10-13, 17, 18, 28, 30, and 33 are canceled herein. Although Applicants disagree that any of the claims were directed to non-statutory subject matter, in the

interest of moving the present application toward allowance, applicants have amended claims 3, 6, 14, 16, 29, and 31 to include the term "isolated," as helpfully suggested by the Examiner. Claim 32 depends from claims 14, 16, and 29, so also incorporates the "isolated" limitation. Applicants submit that this obviates the rejection.

35 USC § 112, second paragraph

Claims 17, 18, and 30 were rejected as allegedly being indefinite. Applicants have canceled these claims. Therefore, the rejection is moot.

35 USC § 112, first paragraph

Claims 1, 2, 4, 5, 7, 8, 21-23, and 28-32 were rejected as allegedly lacking enablement. The Office action states, at page 7, that "[t]he specification does not enable any person skilled in the art . . . to make and use the invention commensurate in scope with these claims."

In the interest of moving the present application toward allowance, applicants have canceled claims 1, 2, 4, 5, 23, 28, and 30, thus obviating the rejection as to these claims. Claims 7, 21, and 22 have been amended to depend solely from claim 3 and/or claim 6, neither of which was included in this rejection. As preparation of humanized antibodies (claim 7) and of pharmaceutical compositions (claims 21 and 22) is routine in the art, applicants request withdrawal of the rejection of claims 7, 21 and 22, as amended.

Claim 29 recites antibodies comprising a heavy chain variable region having CDRs 1, 2, and 3 comprising the sequence of SEQ ID NO: 123, 124, and 125, respectively, and a light chain variable region having CDRs 2 and 3 comprising the sequence of SEQ ID NO: 144 and 158, respectively and CDR1 comprising one of SEQ ID NOs: 174-188. The heavy chain variable region CDRs correspond to those of the heavy chain of SEQ ID NO: 90, and the light chain CDRs correspond to those of the light chains of SEQ ID NO: 191-205. The binding activities of antibodies having a heavy chain of GC33.ver.k (SEQ ID NO: 90) and light chains of SEQ ID NO: 191-205 are described in Example 25. Further, the Office action acknowledges at page 7 that the specification provides enablement for "GC33 L chains comprising SEQ ID NO: 191,

192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204 or 205 paired with humanized, GC33 H chain of ver.k (SEQ ID NO: 90)." Applicants submit that the antibodies recited in claim 29 are fully enabled by the specification, and request withdrawal of the rejection.

Claim 32 as amended depends from claims 14, 16, and 29, all of which have a scope acknowledged by the Office as being enabled. Applicant requests withdrawal of the rejection of claim 32.

Claim 8 as amended recites isolated antibodies comprising the CDRs of GC33 with a single amino acid residue (among all of the CDRs) substituted, deleted, added or inserted. New claim 35 recites isolated antibodies having a VH comprising SEQ ID NO: 84, 85, 86, 87, 88, 89 or 90 and a VL comprising SEQ ID NO: 92, with one amino acid residue substituted, deleted, added, or inserted in either the VH or VL. Claim 31 recites isolated antibodies comprising a VL region of any of SEQ ID NOs: 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204 and 205 paired with a VH region of any of SEQ ID NOs: 84, 85, 86, 87, 88, 89 or 90. SEQ ID NOs: 191-205 vary at one CDR amino acid residue, whereas SEQ ID NOs: 84-90 vary by substitution of up to five FR amino acid residues.

The available art at the time of filing of the application acknowledged that many single-amino-acid-residue changes can be made in the CDRs and FRs of antibodies without significantly affecting binding activity. In fact, Pascalis et al., cited by the Office, teaches that "Examination of the known structures of Ab-Ag complexes reveals that only one-third of the CDR residues are involved in the interaction with Ag" (page 3080, col. 1). This suggests that most residues can be changed without inducing a substantial change in binding specificity.

Of the references cited by the Office with regard to substitution of amino acid residues of antibodies, Brummel et al. and Kobayashi et al. both relate to modification of residues that were identified as key for binding. These changes would, of course, be expected to alter binding. Just as it is possible deliberately to select key binding residues for alteration, it is also possible to choose not to alter those key residues and instead select others that are not key. Even when random changes are made, Pascalis et al. would suggest that two-thirds of the changes would have no effect on binding specificity. The test for enablement is not whether it is possible to

make changes that destroy binding, but rather whether it is possible to make embodiments that would work (see, e.g., *In re Wands*, cited in the Office action). Clearly the answer to that is yes, and it would be routine to do so.

Further, the applicability of the references cited by the office regarding amino acid substitutions is not clear. The claimed antibodies bind to glypican 3, which is a protein. Of the references, only Colman et al. relates to modifications to antibodies that bind to protein antigens. Brummell et al. and Brorson et al. relate to carbohydrate antigens, Kobayashi et al. and Jang et al. relate to nucleic acid antigens, and Burks et al. relates to small molecule haptens.

The specification describes several working examples of GC33 variants with one or more amino acid substitutions or insertions in CDRs and/or FRs. Example 24 describes the creation of SEQ ID NOs: 84 to 90, which are functional humanized heavy chain variable regions that differ from each other by up to five amino acid residues in the FRs, and SEQ ID NO: 92, which is a humanized light chain variable region that differs from the mouse light chain (SEQ ID NO: 73) by eight amino acid substitutions and one insertion. Example 25 describes the creation of SEQ ID NOs: 174 to 188, which are functional light chain CDR1 variants that each have one amino acid substitution as compared to SEQ ID NO: 143. Example 24 also demonstrates that VH comprising all of SEQ ID NOs: 84-90 are functional when paired with a VL comprising SEQ ID NO: 92, whereas example 25 demonstrates that VL comprising each of SEQ ID NOs: 191-205 are functional when paired with a VH comprising SEQ ID NO: 90.

The Office action states at page 18, "The specification provides no direction or guidance regarding how to produce the genus of antibodies as broadly defined by the claims." This is simply not the case. The specification provides substantial guidance in how to make and test CDR and FR variant antibodies. Means for modifying antibodies, e.g., for humanization, are described at page 47, line 6, to page 48, line 4, with several references cited. Detailed examples of the preparation of antibody variants are presented in Examples 24 and 25. Several known, standard methods of testing antibody function are described, including surface plasmon resonance, enzyme linked immunosorbent assay (ELISA), an enzyme immunoassay (EIA), a radioimmunoassay (RIA), and fluorescent antibody techniques (page 55, line 10, to page 56,

line 11). Detailed descriptions of the evaluation of binding activity by ELISA (Examples 5, 8, 24, and 25), flow cytometry (Example 9), competitive ELISA (Example 10), and Western blotting (Example 11) are also presented.

The Office action continues on page 18:

> Furthermore, while the level of skill required to generate the antibodies is that of a molecular biologist or molecular immunologist, the artisan of ordinary skill in the art would have been required to characterize the parent antibody, identify candidate amino acid residues for modifications in the FR and/or CDR domains, perform the mutagenesis on the FR and CDR domains, produce and express the modified antibodies, measure binding characteristics (e.g., binding specificity, equilibrium dissociation constant (K_D), dissociation and association rates (K_{off} and K_{on} respectively), and binding affinity and/or avidity compared with the parent antibody) in a BIAcore assay, and then finally perform bioassays to identify any one or more of the characteristics of an antibody. The technology to perform these experiments was available at the time of application filing, but the amount of experimentation required to generate even a single FR- and/or CDR-modified antibody meeting all of the claim limitations would not have been routine much less could one of ordinary skill in the art predict that any one or combination of all the FR and CDR modifications encompassed by the claims would result in just any antibody clone having retained the antigen binding activity. . . .

Applicants respectfully disagree. As a first matter, a thorough BIAcore analysis would not be required to practice the claims. As noted above, any one of several methods can be used to determine the activity of the claimed antibodies. Further, MPEP 2164.06 states that "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." (In re Wands, 858 F.2d 731, 737, 8 USQP2d 1400, 1404 (Fed. Cir. 1988) (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)). Applicants submit that the specification provides significant guidance on making and testing antibody variants (see above). Further, the Office action cites several publications that describe rapid screening methods to identify functional antibody variants that could also be used to make the claimed antibodies (see Vajdos et al., Chen et al., and Wu et al.). In contrast to all this evidence that the experimentation would be merely routine and that the specification provides ample guidance with respect to the direction in which

the experimentation should proceed (thereby fulfilling the test as set forth in MPEP 2164.06), the Office presents no evidence for its assertion that "the amount of experimentation required to generate even a single FR- and/or CDR-modified antibody meeting all of the claim limitations would not have been routine." In fact, the specification describes the generation and testing of several modified antibodies meeting all of the limitations of claims 8, 31, and 35. Applicants submit that, in view of the state of the art at the time of filing, the skill of those in the art, the amount of direction and guidance in the specification, and the working examples, claims 8, 31, and 35 are fully enabled.

Claims 21 and 22 were rejected as allegedly not enabled. The Office action states that undue experimentation would be required for one skilled in the art to use "any one of the anti-glypican 3 antibodies in vivo to inhibit any kind of cell growth or to inhibit any kind of cancer much less a cancer in a human." As discussed above, claims 21 and 22 have been amended to delete the limitations regarding cell growth inhibition and cancer, so this ground for rejection no longer applies to them. However, Applicants note that new claim 43 recites a method for inhibiting cell growth by administering an antibody, and claim 44 recites a method of treating hepatoma by administering to a subject an antibody. Accordingly, Applicants will briefly address the issue raised with respect to original claims 20 and 21 in the context of new claims 43 and 44.

At pages 20-21, the Office action cites several working examples in the specification of cytotoxicity of various antibodies and antitumor activity of antibodies in a mouse model transplanted with a human hepatoma. Inexplicably, the Office action concludes in the face of these working examples that undue experimentation would be required to practice any embodiment not directly exemplified in the specification, even before considering other factors. These results demonstrate that the antibodies have *in vitro* and *in vivo* cytoxicity and further, that they have antitumor effects on human hepatomas. The presence of these several working examples weighs in favor of the enablement of the claims.

The Office action at pages 21-23 cites Voskoglou-Nomikos et al., Dennis, and Seaver as evidence of the unpredictability of *in vivo* therapeutics. The Examiner appears to be of the

opinion that only results comparable to successful Phase II clinical trials are sufficient to demonstrate enablement. This is simply not the case. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) reversed a decision of the Board of Patent Appeals and Interferences that *in vitro* data cannot support *in vivo* applications. See MPEP § 2164.02. The Office action appears to mischaracterize the teachings of Voskoglou-Nomikos et al., which states, "the in vitro cell line and human xenograft models may be useful in predicting the Phase II clinical trial performance of cancer drugs" (abstract). Additionally, the Office action acknowledges that Seaver teaches that human cancer xenograft mouse models for testing new drugs have been and will remain the industry standard or model of choice for testing of anti-cancer agents. As discussed above, the instant specification provides *in vitro* results and human xenograft mouse models, both of which are recognized as useful in predicting clinical results or are considered "the industry standard or model of choice." Applicants submit that these results, together with the other guidance in the specification and the knowledge in the art at the time of filing, are more than sufficient to support the enablement of the newly added claims.

Priority

Applicants submit herewith a certified translation of the Japanese language priority document, JP 2004-203637, filed July 9, 2004.

35 USC § 102

Claims 9-18 and 33 were rejected under 35 USC § 102(b) as allegedly being anticipated by Aburatani et al. (EP 1 411 118). Claims 9-13, 17, 18, and 33 are canceled herein, and claims 14-16 have been amended to recite isolated antibodies. The Office action states at pages 25-26:

> A polyclonal antibody of Aburatani could reasonably be expected to bind any epitope falling within the structure of human GPC3 including the C-terminus. Thus it is generally expected that within a heterogeneous population of polyclonal antibodies, some could be found that would bind to a peptide consisting of . . . residues 546-551 of GPC3 . . . . Further within the heterogeneous population of polyclonal antibodies, some could be found that

> could bind the same epitope as the GC33 antibody or an antibody comprising the CDRs of GC33. One would readily envisage that the antibody of Aburatani has the same properties of binding GPC3 and that humanized forms could be made therefrom.

Applicants note that such speculation about what might have been present in an uncharacterized mixture of antibodies such as the polyclonal antibody of Aburatani does not constitute evidence that the presently claimed antibodies are anticipated by Aburatani. As the Examiner is no doubt aware, anticipation requires that the claimed composition have necessarily been present in the prior art, even if not appreciated at the time. Accordingly, the Office has not made out a proper case of anticipation justifying rejection of any of the present claims. Nonetheless, in order to move the claims to allowance, applicants have amended the claims to specify that the antibody is "isolated." Aburatani et al. does not teach or suggest the isolated antibodies as recited in amended claims 14 and 16; the antibodies cited by the Office action are polyclonal. Therefore, claims 14 and 16 are novel over Aburatani et al.

Claims 10-14, 16, and 33 were rejected under 35 USC § 102(b) as allegedly being anticipated by Gonzalez et al. (J. Cell Biol. 141:1407-14, 1998). Claims 10-13 and 33 are canceled herein, and claims 14 and 16 are amended to recite isolated antibodies. The Office action states at pages 26-27:

> Gonzalez discloses generating sheep polyclonal antibodies against a human GPC3 fragment containing the last 70 amino acids (i.e., residues 511-580) (M & M, p. 1408, Col. 2, ¶ 7). A polyclonal antibody of Gonzalez could reasonably be expected to bind any epitope falling within the structure of the 70 amino acid residues of the C-terminal fragment of GPC3. Thus it is generally expected that within a heterogeneous population of polyclonal antibodies, some could be found that would bind to a peptide consisting of . . . residues 546-551 of GPC3 . . . . Further within the heterogeneous population of polyclonal antibodies, some could be found that could bind the same epitope as the GC33 antibody or an antibody comprising the CDRs of GC33.

Similar to Aburatani et al., Gonzalez et al. does not teach or suggest the isolated antibodies as recited in amended claims 14 and 16; the antibodies cited by the Office action are polyclonal. Therefore, claims 14 and 16 are novel over Gonzalez et al.

Claims 10-14, 16, and 33 were rejected under 35 USC § 102(b) as allegedly being anticipated by Pilia et al. (Nature Genetics 12:241-247, 1996). Claims 10-13 and 33 are canceled

herein, and claims 14 and 16 are amended to recite "isolated" antibodies. The Office action states at page 28:

> Pilia discloses producing rabbit polyclonal antibodies generated against 4 peptide sequences described as having "marked hydrophobic character" and one of which corresponds to residues 533-547 of human GPC3, specifically, DDAPGNSQQATPKDN (p. 247, Col. 1, ¶ 3). The peptide of Pilia is overlapping in whole or in part with the peptides of Claims 10-14 and 33. It is generally expected that within a heterogeneous population of polyclonal antibodies, some could be found that would bind to a peptide consisting of . . . residues 546-551 of GPC3 . . . . Further within the heterogeneous population of polyclonal antibodies, some could be found that could bind the same epitope as the GC33 antibody or an antibody comprising the CDRs of GC33.

As above, Pilia et al. does not teach or suggest the isolated antibodies as recited in amended claims 14 and 16; the antibodies cited by the Office action are polyclonal. Therefore, claims 14 and 16 are novel over Pilia et al.

Claims 3, 7, 9-18 and 33 were rejected under 35 USC § 102(e) as allegedly being anticipated by Aburatani et al. (WO 2004/022739, published 3/18/04; filing date 9/4/03; priority date 9/4/02).[1] Claims 9-13, 17, 18, and 33 are canceled herein, mooting the rejection with regard to these claims. The Office action states at page 30:

> Aburatani discloses . . . generating polyclonal or monoclonal antibodies against C-terminal fragments, for example [0035-0038]. It is generally expected that within a heterogeneous population of polyclonal antibodies, and even amongst a pool of monoclonal antibodies, that some could be found that would bind to a peptide consisting of . . . residues 546-551 of GPC3 . . . . Further within the heterogeneous population of polyclonal antibodies, some could be found that could bind the same epitope as the GC33 antibody or an antibody comprising the CDRs of GC33. One would readily envisage that the antibodies of Aburatani could have the same properties of binding GPC3.

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[1] For the record, applicants point out that Aburatani et al. is not available as 102(e) prior art against the present claims. Section 102(e) provides that "an international application filed under the treaty defined in section 351(a) shall have the effects for the purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language" (applicants' emphasis). Although Aburatani et al. is an international application that designated the United States, Aburatani et al. was published in Japanese. Therefore, Aburatani et al. is not available as prior art under section 102(e). See MPEP § 2136.03 II. However, Aburatani et al. is citable on its face as prior art under section 102(a), because it was published before the July 9, 2004, priority date of the present application.

As above, Aburatani et al. does not teach or suggest the isolated antibodies as recited in claims 3, 7, and 14-16; the antibodies cited by the Office action are polyclonal. Therefore, claims 3, 7, and 14-16 are novel over Aburatani et al.

Double Patenting

Claims 9-15, 17, 18, and 33 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being allegedly unpatentable over claims 9 and 23-29 of copending Application No. 10/526,741. Claims 9-13, 17, 18, and 33 are canceled herein. Applicants request that the rejection be held in abeyance with regard to claims 14 and 15 and re-addressed once the final scope of these claims has been determined.

Claims 9 and 15 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being allegedly unpatentable over claims 1-5 of copending Application No. 11/414,676 in view of Queen (U.S. Pat. No. 5,530,101). Claim 9 is canceled herein, and claim 15 is amended such that it no longer depends from claim 9. Claim 15 now depends from claims 14 and 16, neither of which was rejected for alleged double patenting. Therefore, applicants request withdrawal of the provisional rejection over Application No. 11/414,676 in view of Queen.

CONCLUSION

Applicants submit that all claims are allowable, confirmation of which is requested by the Examiner. Applicants do not concede any positions of the Examiner that are not expressly addressed above, nor do applicants concede that there are not other good reasons for patentability of the presented claims or other claims.

This reply is being submitted with a Petition for Extension of Time and the required fee. The fee in the amount of $1,000 for excess claim fees is being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 19672-003US1.

Respectfully submitted,

Date: September 29, 2008

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